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Segregation of a Paternal Insertional Translocation Results in Partial 4q Monosomy or 4q Trisomy in Two Siblings

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A genetics evaluation was requested for a 6-week-old infant with multiple congenital malformations including mild craniofacial anomalies, truncal hypotonia, hypospadias, and a ventriculoseptal defect. Blood obtained for chromosome analysis revealed an abnormal chromosome 4. Paternal chromosome analysis showed a 46,XY, inv ins (3;4)(p21.32; q25q21.2), inv(4)(p15.3q21.2) karyotype. Therefore, the proband's chromosome 4 was the unbalanced product of this insertional translocation from the father resulting in partial monosomy 4q. Additionally, the derivative 4 had a pericentric inversion which was also seen in the father's chromosome 4. During genetic counseling, the proband's 2-year-old brother was evaluated. He was not felt to be abnormal in appearance, but was described as having impulsive behavior. Chromosome analysis on this child revealed 46, XY,der(3)inv ins(3;4)(p21.32;q25q21.2)pat. This karyotype results in partial trisomy 4q. FISH using two-color "painting" probes for chromosomes 3 and 4 confirmed the G-banded interpretation in this family. The segregation seen in this family resulted in both reciprocal products being observed in the two children, with partial 4q monosomy showing multiple congenital anomalies, and partial 4q trisomy showing very few phenotypic abnormalities.

KEY WORDS: **insertional translocations, fluorescence in situ hybridization, malsegregation, 4q deletion, 4q duplication**

INTRODUCTION

Patients with deletions of 4q have been described in recent literature reports [Cervenka et al., 1976; Bonfante et al., 1979; Lin et al., 1988]. Most patients with a terminal deletion showed a cluster of clinical findings specific enough to identify a unique phenotype [Lin et al., 1988]. In contrast, patients with interstitial deletions have shown a less specific phenotype, although mental retardation and craniofacial anomalies are commonly described [Mitchell et al., 1981, Lin et al., 1988]. An interstitial deletion of 4q is a relatively rare finding [Butler et al., 1987; Rose et al., 1991; Kulharya et al., 1995]. Likewise, there are a limited number of patients with partial trisomy of 4q [Halal et al., 1991; Jeziorowska et al., 1993; Zollino et al., 1995]. We report on a family with unbalanced segregants from a paternal insertional translocation, resulting in two liveborn children, one who is monosomic for 4q21.2-q25, and the other who is trisomic for 4q21.2-q25, with presentation of their phenotypes.

CLINICAL REPORT

Patient 1 (Fig. 1a and b)

A genetics evaluation was requested for a 6-week-old male infant with congenital heart disease, hypospadias, and mildly abnormal facial features. He was born to a 21-year-old G2P2 mother. The early pregnancy was unremarkable, with normal alpha-fetoprotein levels. Decreased fetal movement was noted by 32 weeks gestation, and slowing of fetal growth was seen by 34 weeks. Oligohydramnios was noted by 38 weeks gestation. At 39 weeks, a nonstress test showed fetal bradycardia, and an emergency cesarean section was performed. Apgar scores were 1 at one minute and 7 at five minutes. Initial neonatal resuscitation was required.

On examination, weight was 2.4 kg (25th centile), length was 46 cm (<3rd centile), and OFC was 34 cm (5th centile). Inner and outer canthal distances as well as all facial measurements were at the 25th centile. The face showed short nose, flat philtrum, thin upper lip, mild micrognathia, and protuberant, simple ears. A cardiac murmur was noted on physical exam. Hypospadias was present with bilateral descended testes. Bilateral transverse palmar creases were noted. The neuro-

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Fig. 1. **a, b:** Patient 1 at 6 weeks of age. Note the short nose, ears with indented helix and uplifted lobule, flat philtrum with thin upper lip. Patient 1 at 8 months of age.

logic exam was unremarkable, with normal tone, normal reflexes, and a good suck. An echocardiogram showed a ventriculoseptal defect as well as dilated cardiomyopathy. Peripheral blood was sent for chromosome analysis.

Upon re-evaluation at 5 months of age, the ventriculoseptal defect had closed spontaneously. The cardiomyopathy was stable, requiring no medical treatment. Because of cyanotic episodes due to feeding difficulties and reflux, a fundoplication and G-tube had been placed. Neurologically, the baby was alert and interactive; central hypotonia was present, and the developmental milestones were delayed by 2 months. Apneic episodes persisted and obstructive apnea was likely. A tonsillectomy and adenoidectomy was performed at 13 months of age resulting in no further apneic episodes.

Upon re-evaluation at 15 months of age, the patient was interactive and playful. A developmental assessment showed global developmental delay, with performance at an 8 month level. He was able to roll over, sit with assistance and weight bear on his hands and knees. Verbally, he squealed and babbled. Height and weight remained well below the 5th centile (50th centile for a 4–5 month old), and OFC is less than the 2nd centile (50th centile for a 3 month old).

Patient 2 (Fig. 2)

The family was seen in the genetics clinic for counseling, after cytogenetic results on the proband became available. At this time, the proband's 2-year-old brother was also evaluated. This child was described as behaviorally impulsive; however, he was not felt to be hyperactive or delayed. No abnormal findings were noted on his examination, and his past medical history was unremarkable. His developmental milestones were within normal range, with sitting independently by 8 months and walking by 14 months of age. Blood was obtained for chromosome analysis.

A development assessment performed at 2½ years of age revealed no areas of delay. Nonetheless, at re-evaluation at 3 years, 3 months of age, his impulsive behavior had worsened. He was noted to have a short attention span and inappropriate anger. No formal IQ testing has been done on this child. However, his speech and vocabulary appeared normal, although he could not count beyond 4.

CYTOGENETIC EVALUATION

Chromosomes were studied on the father, the proband, and the proband's brother (Fig. 3). The initial

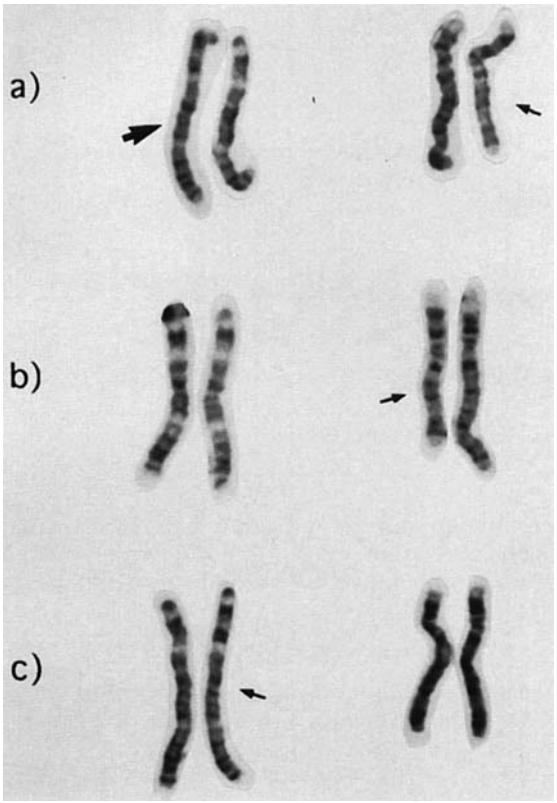

Fig. 2. Patient 2 at 2½ years of age.

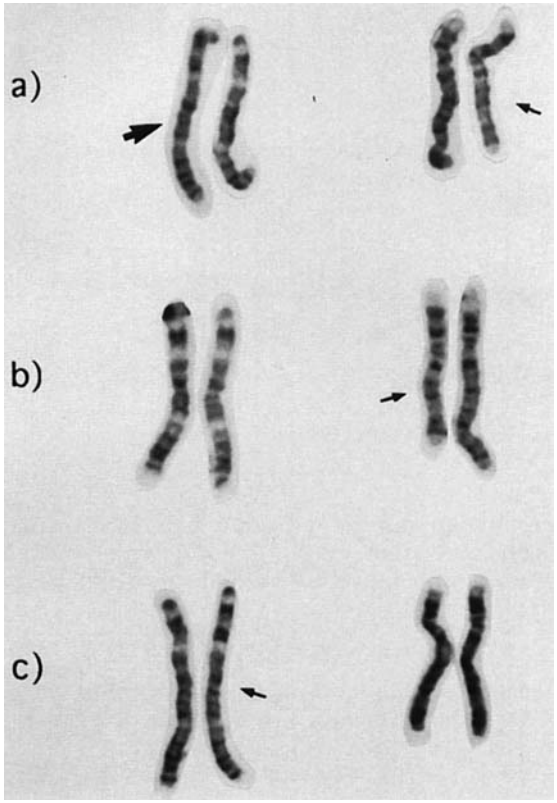

Fig. 3. Partial metaphases showing chromosomes 3 (left) and 4 (right). Abnormal chromosomes are indicated by the arrows. **a:** The father's chromosomes showing an insertional translocation between chromosomes 3 and 4, in which a small segment from 4q was inserted into 3p. In addition, a pericentric inversion in the derivative chromosome 4 is present. **b:** Case 1 showing a deletion in the long arm of chromosome 4 as well as the pericentric inversion in this derivative chromosome 4. **c:** Case 2 showing the derivative chromosome 3, with an insertion of a segment from chromosome 4, resulting in a partial trisomy of chromosome 4q.

cytogenetic evaluation of the proband revealed an abnormal chromosome 4. A deletion in the long arm of one chromosome 4 was apparent, but the exact bands could not be delineated. The parental chromosomes were studied. The mother showed a normal karyotype, 46,XX. The father was found to have an insertional translocation between chromosomes 3 and 4, in which a small segment from 4q was inserted into 3p. In addition, a pericentric inversion in the derivative chromosome 4 was seen. His karyotype was 46,XY,inv ins(3;4)(p21.32;q25q21.2),inv(4)(p15.3q21.2). An ideogram demonstrating the rearrangement in this individual is shown in Fig. 4.

Re-evaluation of the chromosomes in case 1, in light of the father's results, also showed the pericentric inversion in the derivative chromosome 4. Therefore, the proband's karyotype is 46,XY, der(4)inv ins(3;4)(p21.32;q25q21.2),inv(4)(p15.3q21.2)pat. The chromosome analysis in the 2-year-old brother showed only the derivative 3 chromosome, with the insertion of the segment from chromosome 4. This was the reciprocal unbalanced product, resulting in a partial trisomy of chromosome 4.

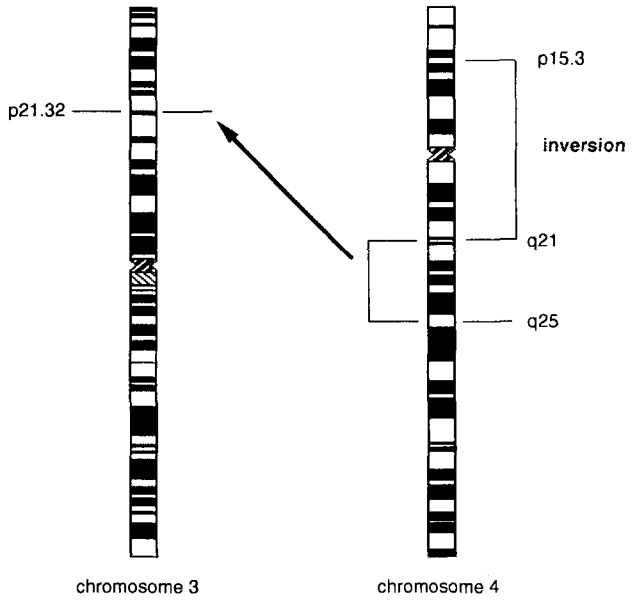

Fig. 4. Ideogram showing the rearrangement between chromosomes 3 and 4 found in the father. His karyotype is 46,XY, inv ins(3;4)(p21.32;q25q21.2),inv(4)(p15.3q21.2).

His karyotype is described as 46,XY,der(3)inv ins(3;4)(p21.32;q25q21.2)pat.

Fluorescence In Situ Hybridization Studies (FISH)

FISH was performed on the chromosome preparations from the father and both children (Fig. 5). An experiment using two color painting probes for chromosomes 3 and 4 was performed according to the manufacturer's specifications (Gibco, BRL). The painting of the father's chromosomes showed hybridization of the chromosome 4 probe to a short segment within chromosome 3, confirming the insertion. The painting probe specific for chromosome 3 hybridized only to both chromosomes 3, confirming the one-way insertional translocation. The same painting probes for chromosomes 3 and 4 were used to confirm the G-banded results in both children.

DISCUSSION

We report on a family in which the father carries an insertional translocation between chromosomes 3 and 4, as well as a pericentric inversion within the derivative chromosome 4. For this man, there are two possibilities for unbalanced products resulting from Adjacent I segregation. One includes inheritance of the derivative 3 and a normal chromosome 4, which results in a partial trisomy of 4q. Alternatively, inheritance of the derivative 4 with the normal chromosome 3 results in a partial monosomy of 4q. Each of these abnormal segregation products were seen in the first two children born to this couple, with no history of known miscarriages. In this translocation, however, pairing would be expected to be difficult between these small segments in Adjacent I segregation.

Another more probable mode of segregation to account for these outcomes is the independent synapsis of

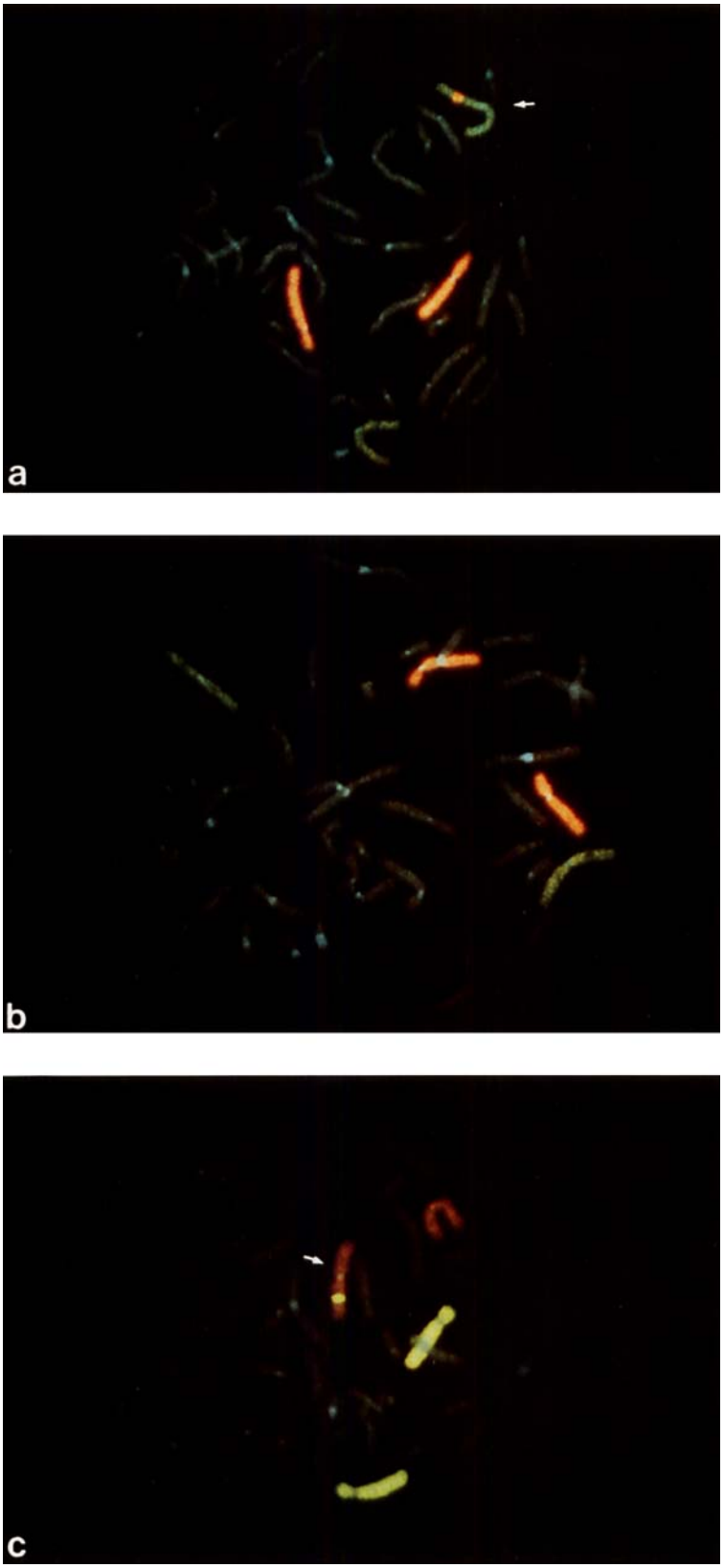

Fig. 5. FISH experiment using two color painting probes for chromosomes 3 and 4. **a:** The father's chromosomes showed hybridization of the chromosome 4 painting probe (red) to a short segment within chromosome 3 (green) (arrow), confirming the insertion. **b:** Using chromosomes 3 (green) and 4 (red) painting probes, Patient 1 showed complete hybridization and no evidence of an insertion, consistent with a deletion of chromosome 4. **c:** Patient 2 showed a normal hybridization pattern of chromosome 4 (green); however, chromosome 3 revealed the insertion of chromosome 4 material into the short arm (arrow), consistent with the G-band interpretation.

homologous pairs, with the pairing of the homologous chromosomes regardless of the insertion. The inserted segment likely loops out, as pairing of this segment is not possible. In this case, "normal" segregation of each chromosome pair is expected, and four possible gametes may be formed randomly in equal proportion: normal, balanced carrier, unbalanced partial trisomy, and unbalanced partial monosomy.

In addition to the insertional translocation, this father also carries a pericentric inversion, which places an additional risk for abnormal conceptuses. This risk is due to the possibility of recombination within the inverted segment, resulting in deletion/duplication of the noninverted segments. However, both possible recombinant chromosomes would not be expected to be viable, due to large imbalances. Therefore, this family may be expected to experience miscarriages.

Insertional translocations have been estimated to occur in 1 in 5,000 newborns [Chudley et al., 1974]. Overall, pooled data from families with insertional translocations reveals a risk of 32% for a child with an unbalanced chromosomal constitution to be born to a known insertional translocation carrier [Walker and Bocian, 1987]. The risk is greater in cases of small segment insertions, and the risk is less in large segment insertions, probably due to greater nonviability in the offspring. Also, if the segment involved in a partial trisomy or monosomy contains few genes, the viability of the unbalanced child will be less affected, and the risk of an abnormal outcome will approach the theoretical risk of 50%. In this family with two identified pregnancies, both have resulted in viable abnormalities, with the segment involved in the partial trisomy/partial monosomy being 4q21.2q25.

Several patients with deletions involving different segments of 4q have been described [Mitchell et al., 1981; Lin et al., 1988]. Patients with 4q terminal deletions share enough similarities to represent an identifiable phenotype [Mitchell et al., 1981; Lin et al., 1988]. These patients' findings included an abnormal skull shape, hypertelorism, cleft palate, low-set pinnae, short nose with an abnormal bridge, pointed fifth finger and nail, congenital heart and genitourinary defects, moderate to severe mental retardation, poor postnatal growth, and hypotonia. In contrast, patients with interstitial deletions of 4q are seen less commonly. Furthermore, these patients do not show enough similarity to represent an identifiable syndrome. This lack of phenotypic correlation may be due to the different segments of 4q involved in the deletion. Although this certainly could account for some of the variability seen, phenotypic variation between patients with interstitial deletions of 4q occurs, even in cases with nearly identical breakpoints [Butler et al., 1987; Rose et al., 1991; Kulharya et al., 1995]. Craniofacial anomalies commonly occur in both interstitial and terminal deletion patients, including abnormal skull shape, hypertelorism, epicanthal folds, and abnormal ears. Our case 1 did not show skull asymmetry or vertebral anomalies, but had some dysmorphic features of the nose, lips, ears, and mild micrognathia. Additionally, he had a ventriculoseptal defect and developmental delay. The renal cysts, seen in some patients with monosomy 4q, were initially seen in this patient on a prenatal ultrasound. However, a follow-up renal ultrasound performed in the perinatal period showed no further evidence of these cysts. Thus, the patient in case 1 shared only some rather general, nonspecific features with other interstitial monosomy 4q patients.

In comparing case 2 with partial trisomy 4q cases in the literature, there is a limited number of partial trisomy 4q patients described. The majority have been ascertained due to familial balanced translocations [Bonfante et al., 1979]. Only a few cases have been described involving trisomy for an interstitial segment of 4q. The phenotypic features have been summarized recently [Halal et al., 1991; Jeziorowska et al., 1993; Zollino et al., 1995].

In general, duplications of the distal half of 4q cause more severe anomalies as compared to more proximal duplications. However, patients with duplications of 4q frequently have mental retardation, growth retardation, microcephaly, epicanthal folds, low set and/or malformed ears, short philtrum, and thumb abnormalities [Halal et al., 1991; Jeziorowska et al., 1993; Zollino et al., 1995]. Currently, there are no other patients reported who are trisomic for only the limited segments of 4q21.2→q25 as our case 2.

In a recent review of nine patients trisomic for various interstitial segments of 4q, a comparison was made of the findings seen in each patient with the segment of 4q involved [Zollino et al., 1995]. Renal hypoplasia and thumb abnormalities were found in all nine patients who had a trisomic segment involving 4q21q22. This led the authors to postulate existence of a developmental gene in this region involved in defining the acrorenal field, with a developmental field defect resulting from the imbalance in these patients. Our patient (case 2) is also trisomic for this region, but does not show any evidence of thumb abnormalities. He does not appear to have any evidence of organ system involvement. In fact, his mild phenotype is in contrast to the significant findings seen in these other trisomy 4q patients. All patients trisomic for any segment of 4q showed some degree of psychomotor retardation. Our patient was seen at another institution for a full developmental assessment, with no delays found in gross motor, fine motor, or language skills at 2½ years of age.

The use of fluorescence in situ hybridization "painting" probes to clarify the chromosomal rearrangement was very helpful in this family. Painting probes in general can be useful in clarifying whether a derivative chromosome is the product of a reciprocal translocation, or results from a more complex chromosomal rearrangement [Spikes et al., 1995]. As this technique becomes more widely used, more accurate assessment of complex rearrangements can be anticipated. This case illustrates the need for thorough family evaluations in cases of translocations to ascertain all affected family members and to offer accurate recurrence risks.

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